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Biosimilars: Imitation Games

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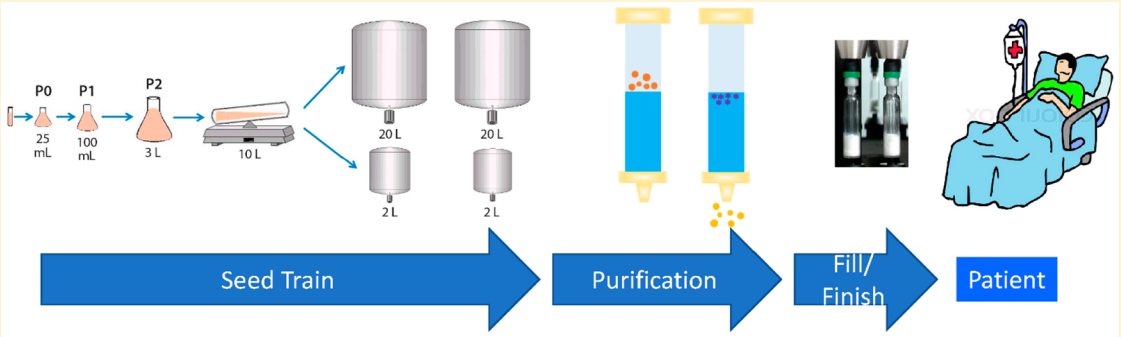

ABSTRACT: Biopharmaceutical sales were at $160 billion in 2016. With many top revenue biopharmaceuticals coming off patent in the next 4 years, there is a tremendous rush by leading biopharmaceutical companies worldwide to launch biosimilar versions of innovator products. However, these protein drugs are extremely difficult to copy. In this viewpoint, we will discuss the various drugs slated to lose patent protection and the challenges in manufacturing these drugs using current technologies. The Food and Drug Administration's regulatory role and definitions of similarity will be discussed, and finally, the scientific challenges in mimicking a protein drug in the current patent- and innovation-driven research field will be considered.

Biosimilars are therapeutic protein-based molecules that gain approval based on demonstrating similarity to an approved biological product, according to specifications stated by the Food and Drug Administration (FDA). The primary specification is demonstration of "no clinically meaningful differences in terms of safety and effectiveness from the reference product."[1] Today, the average daily cost of biopharmaceutical drugs is ~$45, much higher than the ~$2 for small-molecule drugs.[2] Much like the Hatch−Waxman Act (1984) provided a legal and regulatory pathway for generic drug competition while still providing incentives for innovation from small-molecule drug manufacturers, the Biologics Price Competition and Innovation Act (BPCIA) of 2009 is intended to do the same for biologics and biosimilars. Biologic therapies have revolutionized treatment of patients with serious diseases, including hematological (anemia, hemophilia) or autoimmune (rheumatoid arthritis, Crohn's disease) disorders and cancers.[3] As patents for many biologics expire, biosimilar agents will become available, offering affordable and increased access to biological therapies for a wider population worldwide. In 2006, the FDA approved Omnitrope, which was dubbed a "follow-on biologic," insinuating that this was a special case. It was the approval of filgrastim-sndz, (Zarxio, Sandoz), by the US FDA on March 6, 2015, that marked the first entry of a biosimilar into the US market. Since then, several biosimilars have been approved (Table 1). With many blockbuster biopharmaceuticals recently coming off patent and several more by 2020 (Figure 1), there has been a surge of interest worldwide from generic drug companies (e.g., Mylan and Sandoz), dedicated biosimilar manufacturers (e.g., Coherus and Celltrion), and traditional innovator biopharmaceutical companies (e.g., Biogen and Amgen) in entering the biosimilars fray.

Table 1. List of All Biosimilars Approved by FDA in the USA (Compiled 5/11/2017)

date of approval	biosimilar	original
6-Mar-15	Filgrastim-sndz (Zarxio)	filgrastim (Neupogen)
5-Apr-16	infliximab-dyyb (Inflectra)	infliximab (Remicade)
30-Aug-16	etanercept-szzs (Erelzi)	etanercept (Enbrel)
23-Sep-16	adalimumab-atto (Amjevita)	adalimumab (Humira)
21-Apr-17	infliximab-abda (Renflexis)	infliximab (Remicade)

THE CHALLENGE OF BIOSIMILARS

Currently, over 200 biological drugs have been successfully commercialized, including hormones such as insulin and human growth hormone, hematopoietic factors such as erythropoietin and granulocyte colony-stimulating factor (G-CSF), enzymes to treat metabolic disorders such as Gaucher disease, immunomodulatory factors such as interferons (IFN) and interleukins, and a wide range of monoclonal antibodies such as rituximab and trastuzumab, treating autoimmune diseases, cancer,

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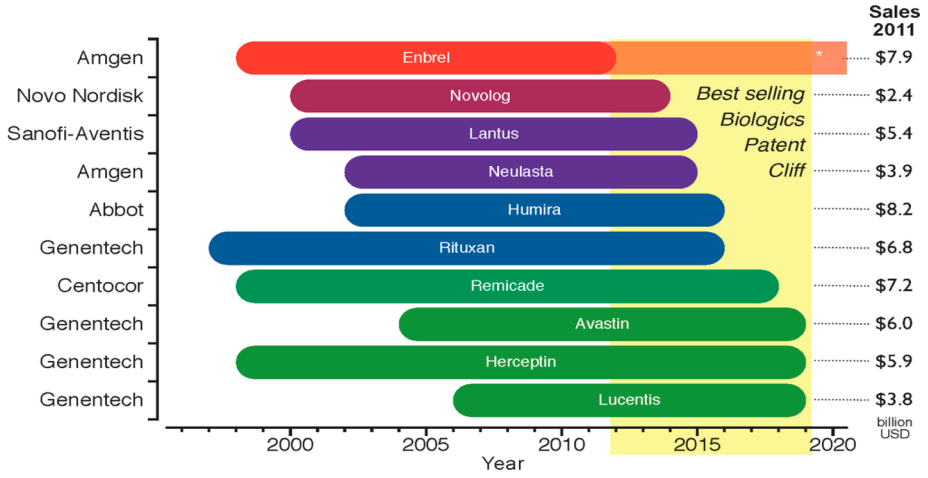

Figure 1. Blockbuster drugs scheduled to come off patent by 2020. Used with permission from ref 4. Copyright 2012 MDPI.

infectious disease, and a host of other conditions. Because of the size and complexity of biopharmaceutical drugs, chemical synthesis is currently not possible. Biopharmaceutical drugs are therefore derived from a complex procedure involving recombinant DNA technology and culture of specialized cells. After cell transfection with the DNA sequence encoding the recombinant protein and clonal selection of the desired cells, the protein production process begins by scaling up the cells into a fermentation vessel where the protein is expressed at commercially viable titers. Multiple sequential steps for purification, validation, and formulation deliver a purified protein that is efficacious and stable for patient administration.

Biotherapeutics are substantially larger than traditional pharmaceuticals. A common example of a traditional pharmaceutical is aspirin, with a molecular mass of 180 Da. In comparison, first-generation biologics like insulins and hormones are ∼10 000 Da, and the most complex biologics, e.g., monoclonal antibodies, are in the range of 145 000−160 000 Da. In addition to their much larger size, proteins are chemically much more complicated and diverse, being composed of 20 different amino acids with a wide range of size and functionality. Beyond the protein sequence itself, proteins are subject to various post-translation modifications (e.g., glycosylation, phosphorylation, and carboxylation) that impact function, stability, and immunogenicity. From the FDA-approval perspective, characterization of these large, complex, and variable macromolecules presents a serious challenge. Knowledge of sequence and structure is not sufficient to characterize the biomolecules. Due to the permutations of chemical modifications, large macromolecules remain challenging to completely characterize with the current available tests. The use of living cells to manufacture these biomolecules further adds a dimension of variability that is difficult to regulate. In addition to the complexity of the process itself, to make commercially viable product, every innovator may have utilized engineered cells and various degrees of optimization to known fermentation and purification protocols. Therefore, it has been argued that the process of generating biosimilars may be daunting.

WHAT IS SIMILAR ENOUGH?

In Europe, Canada, and Japan, biosimilars are approved through established regulatory pathways. The European Medicines Agency (EMEA) is the leading authority in regulation of biosimilar approval in the European Union (EU). In India, biosimilar approval is semiregulated and no phase I/II studies are required.[5] Since 2007, biosimilars have been marketed in the EU, and their specifications provide instructive insight into understanding regulatory guidelines addressing similarity. Customized guidelines exist for specific classes of biosimilars, related to manufacturing quality, nonclinical pharmacology and toxicology, and pharmacokinetics and clinical considerations.[6] The products where specific guidance has been issued include erythropoietin, G-CSF, insulin, growth hormone, and IFNα. Some key issues addressed by the EMEA guidelines are safety, immunogenicity, clinical efficacy, and extrapolation of indications. The guidelines state explicitly that when the safety of biosimilars is being assessed, identical safety parameters to those used when the innovator product was originally evaluated must be applied in the development program. There should also be a sufficient patient sample size in the clinical trial program to quantify the adverse effect profile relative to the reference product. The EMEA guidelines also put an emphasis on a well-designed pharmacovigilance program following approval in order to assess potentially serious events that may occur with very low frequency.

For expression of a therapeutic protein, the FDA approves various cell lines that are designated GRAS (generally regarded as safe). For expression of recombinant proteins that require correct post-translation modifications, Chinese hamster ovary (CHO) cells have been the preferred cell line in the biotechnology industry. CHO cell-line engineering is often performed industrially to improve productivity and quality attributes. These engineering efforts have led to improvements in cell growth and protein expression and quality. As our understanding of glycosylation and analytical tools become more sophisticated, we appreciate the role of host cell selection in influencing protein quality. However, recent research has shown that individual antibody glycoform(s) may provide optimal efficacy for selected outcomes. Thus, a further challenge will be the production of biosimilars aiming for select clinical indications. In addition, the protein quality may undergo changes as a result of cell adaptation to various fermentation conditions,[7] final buffer environment,[8] and storage,[9] all of which may be proprietary information. While small changes in these parameters can impact the various chemical permutations for a given biotherapeutic, innovators

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can, under certain circumstances, change the host cell, fermentation process, purification process, and even manufacturing site, but the product can be validated without undertaking a complete new product development review. Similar principles can apply to the FDA's review of biosimilars. For over 20 years, the FDA has worked with manufacturers to implement manufacturing changes without requiring additional clinical trials due to the substantial expense. New advances in analytical sciences have the potential to assess protein structures and post-translational modifications, and identify impurities (from any process-related changes) using tests that are vastly more sensitive than clinical trials.[10]

In the age of rapid technological advancements, the tests and assays specified by the originator may be outdated. Even if the biosimilar profile differs from the reference product, higher expectations for analytical tests mean that biologics can be better characterized and increased sensitivity can identify potential impurities. Standard analytical tests for recombinant proteins include:

- Gel electrophoresis
- Conformational analyses
- Amino acid sequence analysis
- Aggregate quantitation
- Normal or reversed phased chromatographic analysis
- Carbohydrate characterization
- Peptide mapping
- Isoelectric focusing to determine charge heterogeneity
- Size exclusion chromatography
- Impurity profile
- Bioassay/function
- Degradation/stability

While the FDA will not give biosimilar manufacturers access to reference product specifications, the commercially available reference product can be used by companies to compare with their biosimilar candidates, albeit at significant expense. Critical quality attributes (CQA) and their specifications are based on the biosimilar manufacturers' analysis of multiple samples (generally from many lots and different manufacturing sites) of commercially available reference product. In general, the FDA has a strong preference for innovator material marketed in the United States as a basis for comparison, but with adequate scientific justification, other comparisons can be employed. FDA review and approval of the biosimilar depends on the report of the comparability of the product to the reference. While the original innovators data will not be disclosed by the FDA, each specification that the biosimilar sponsor generates will need to adhere to conformity of the range of measurements of original product. Every biotherapeutic manufacturer documents in-process parameters, compliance with good manufacturing practices, and adherence to FDA regulations to ensure that product quality is not influenced by variations in set parameters. It is expected that biosimilar manufacturers will demonstrate consistency and control over the manufacturing process, just as is required for innovator products today to avoid any chemical, structural, and functional differences between lots.

FINAL COMMENTS

The US FDA biosimilar pathway was initially proposed in February 2012, with finalized guidance documents issued in 2015. Since then, there have been updates addressing labeling (2016) and a draft guidance on interchangeability (2017). The biotechnology industry is innovation driven and patent conscious. Therefore, it has been commented that the information that defines process parameters and product quality influencers is incomplete or unavailable. This lack of information has led to criticism that the FDA's "purple book"[11] cannot truly reflect all the necessary information that defines the product intended to be regulated. Some biosimilar databases[12,13] provide an overview, but additional resources are much needed. Innovators for biologics employ their own cell lines (adapted or engineered), use proprietary media, and have confidential process steps and optimized downstream steps. These are challenging obstacles to overcome in an already complex process. Recently, an Industry−University Cooperative Research Center (Advanced Mammalian Biomanufacturing Innovation Center (AMBIC)) and an advanced manufacturing institute (National Institute for Innovation in Manufacturing Biopharmaceuticals (NIIMBL)) have been established to understand industrially relevant biology and standardize bioprocess variables.

Now that the US FDA has a regulatory pathway for approval of biosimilars as mandated by the BPCIA, it will be interesting to see whether biosimilars have the same impact in the biologics drug market that generics have had in the chemical drug market. The ultimate success of biosimilars and their potential to reduce healthcare costs will depend, in part, on collecting information pre- and postapproval to address the many uncertainties associated with replicating biologics. However, the role of intellectual property and the higher cost of goods in producing a biological drug compared with a small-molecule drug will certainly influence commercialization of biosimilars as well. Let the games begin.

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Notes

Views expressed in this editorial are those of the authors and not necessarily the views of the ACS.

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REFERENCES

(1) Lynch, H. F.; Cohen, I. G. *FDA in the Twenty-First Century*; Columbia University Press, 2015.

(2) Van Arnum, P. Biosimilars: Market Weaknesses and Strengths Biosimilars represent an emerging niche in the biopharmaceutical market, but how strong is their true potential? http://www.pharmtech.com/biosimilars-market-weaknesses-and-strengths.

(3) Ueda, T. Next-generation optimized biotherapeutics — A review and preclinical study. *Biochim. Biophys. Acta, Proteins Proteomics* **2014**, *1844* (11), 2053−2057.

(4) Calo-Fernandez, B.; Martinez-Hurtado, J. *Pharmaceuticals* **2012**, *5*, 1393.

(5) Reichert, J. M.; Beck, A.; Iyer, H. European Medicines Agency workshop on biosimilar monoclonal antibodies. *MAbs* **2009**, *1* (5), 394−416.

(6) Tsiftsoglou, A. S.; Ruiz, S.; Schneider, C. K. Development and Regulation of Biosimilars: Current Status and Future Challenges. *BioDrugs* **2013**, *27* (3), 203−211.

(7) Ivarsson, M.; Villiger, T. K.; Morbidelli, M.; Soos, M. Evaluating the impact of cell culture process parameters on monoclonal antibody N-glycosylation. *J. Biotechnol.* **2014**, *188*, 88−96.

DOI: 10.1021/acsmedchemlett.7b00199
ACS Med. Chem. Lett. 2017, 8, 690−693

(8) Chaudhuri, R.; Cheng, Y.; Middaugh, C. R.; Volkin, D. B. High-Throughput Biophysical Analysis of Protein Therapeutics to Examine Interrelationships Between Aggregate Formation and Conformational Stability. *AAPS J.* **2014**, *16* (1), 48−64.
(9) Razinkov, V. I.; Treuheit, M. J.; Becker, G. W. Accelerated Formulation Development of Monoclonal Antibodies (mAbs) and mAb-Based Modalities. *J. Biomol. Screening* **2015**, *20* (4), 468−483.
(10) Schiestl, M.; Stangler, T.; Torella, C.; Cepeljnik, T.; Toll, H.; Grau, R. Acceptable changes in quality attributes of glycosylated biopharmaceuticals. *Nat. Biotechnol.* **2011**, *29* (4), 310−312.
(11) USFDA. Purple Book: lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm.
(12) Kozlowski, S.; Woodcock, J.; Midthun, K.; Behrman Sherman, R. Developing the nation's biosimilars program. *N. Engl. J. Med.* **2011**, *365* (5), 385−388.
(13) Niosi, J. Biosimilars in North America. *Technol. Anal. Strateg. Manag.* **2017**, *29* (3), 290−299.

DOI: 10.1021/acsmedchemlett.7b00199
ACS Med. Chem. Lett. 2017, 8, 690−693